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Does COVID-19-related viral sepsis stimulate angiotensin II levels more than bacterial sepsis?

Angiotensin II in the COVİD-19 vs bacterial sepsis

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Abstract
Aim: Angiotensin II and its receptors play a role in both COVID and bacterial sepsis. The aim of this study was to compare the levels of serum angiotensin II and its receptors in viral sepsis due to COVID-19 with the levels in bacterial sepsis.
Material and Methods: The study included 62 sepsis patients (n=31 COVID and n=31 non-COVID) with similar disease severity in the tertiary ICU. The serum angiotensin II, angiotensin II receptors 1 and 2 (ATR1, ATR2) and other inflammatory parameters were measured. Demographic data and 28-day mortality were recorded.
Results: Angiotensin II level was significantly higher in COVID patients than in non-COVID patients ($p<0.05$). ATR1 and ATR2 did not differ between the two groups. There was a negative correlation between angiotensin II and procalcitonin levels in all patients, and a positive correlation between ATR1 and procalcitonin, APACHE II score, and SOFA score in COVID patients ($p<0.05$).
Discussion: Observation showed that angiotensin II levels were higher in patients with COVID-19 compared to those with bacterial sepsis, and ATR1 level was higher in COVID-19 patients who died. It was thought that the renin-angiotensin cascade could be stimulated differently in bacterial sepsis compared to viral sepsis due to COVID.

Keywords
Angiotensin II, Bacterial Infection, COVID-19, Sepsis

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Introduction

Sepsis is a public health problem with high morbidity and mortality. Bacterial, fungal, viral, and parasitic microorganisms can be causative agents. Many pathways are blamed or take part in its pathogenesis [1-3]. There are many studies showing that the renin-angiotensin-aldosterone system (RAS) and related angiotensin II and its receptors play a role in the pathogenesis of bacterial sepsis and septic shock [4-7]. The demonstration that treatment with RAS component inhibitors (angiotensin converting enzyme inhibitors, angiotensin receptor blockers, etc.) can have positive effects in the treatment of patients with COVID-19 during the COVID-19 pandemic has caused angiotensin II and its receptors to be the focus of attention in patients with COVID-19 [8]. However, there is no clinical study in the literature comparing the mediators of the renin-angiotensin system between bacterial sepsis and viral sepsis due to COVID-19.

The aim of this clinical observational study is to examine the changes in serum angiotensin II and its receptors in patients with viral sepsis associated with COVID-19 who are followed up and treated in the intensive care unit, and in patients with bacterial sepsis, which we frequently see in intensive care units.

Material and Methods

This study was carried out in the COVID-19 intensive care and reanimation intensive care units of a university hospital following the approval of the local ethics committee (2021/89). Both intensive care units were followed by the same team, and the same clinical approaches were applied to all patients. From among patients in the two intensive care units, patients with similar disease severity were included in the study. The study included 31 COVID-19 patients whose diagnosis was confirmed by PCR (+) and who were followed up in the COVID-19 intensive care unit due to sepsis, and 31 patients who were hospitalized in the reanimation intensive care unit and were not considered to have COVID-19 according to PCR test, thorax CT findings, and clinical symptoms, did not previously have COVID-19, and where culture confirmed the presence of bacterial sepsis.

The primary outcome of the study was serum angiotensin II, angiotensin II receptor 1 and 2 (ATR1, ATR2) levels. Ten ml of blood was collected from sepsis clinic patients from both intensive care units and centrifuged at 4000 rpm for 10 minutes. Sera separated after centrifugation were placed in polypropylene tubes and stored at -80°C until analysis. The analysis was performed using the ELISA method in accordance with the procedure in the package insert. At the same time, the PaO_2/FiO_2 ratios, C-reactive protein (CRP), procalcitonin, D-dimer, troponin, ferritin, and IL-6 levels of the patients were measured and recorded. In addition, patients' age, gender, comorbidities, source of infection, need for vasopressors, Sequential Organ Failure Assessment (SOFA) score, Acute Physiology, Assessment and Chronic Health Evaluation 2 (APACHE II) score, and 28-day mortality were recorded. The oxygen delivery method and whether the patients received steroids, tocilizumab, and other anti-inflammatories were recorded.

When the sample size was determined with effect size 0.7, α error probability 0.05, and power 0.8 with the G Power 3.1.9.4 program, the total sample size was found to be 52. The data of 62 patients were included in the study. With the data obtained at the end of the study, power analysis was evaluated with the biostatapps.inonu.edu.tr/WSSPAS/ program, and the effect size was evaluated as 1.34 and power as 0.99 [9].

IBM SPSS Statistics 22 program was used for statistical analysis. The suitability of the parameters to the normal distribution was evaluated with the Levene test. While evaluating the study data, quantitative data were compared as well as descriptive statistical methods. Student's t-test was used for the comparison of normally distributed parameters between groups, and the Mann-Whitney U test was used for the comparison of non-normally distributed parameters. The Chi-square test and Fisher's Exact Chi-square test were used to compare qualitative data. Significance was evaluated at the $p<0.05$ level.

Ethical Approval

Ethics Committee approval for the study was obtained.

Results

There was no significant difference between the patients in terms of demographic data. All patients except two of the

Table 1. Demographic and laboratory data of groups.

	COVID-19 (n=31)	Non-COVID (n=31)	P value
Age (year, mean±SD)	71.10±15.20	70.27±16.13	0.837
Gender (M/F)	18/13	12.19	0.127
APACHE score (mean±SD)	19.48±6.81	20.53±7.02	0.556
SOFA score (mean±SD)	7.39±3.44	7.20±3.10	0.824
Vasopressor	10.31	11.31	0.717
Ventilation			
Nasal cannula	3	14	0.001*
HFNC/NIV	14	0	
Invasive mechanical ventilation	14	15	
Steroid using	29/31	0/31	0.001*
Mortality	20/31	20/30	0.79
Co-existing disease			
Hypertension	2	2	0.17
Diabetes mellitus	6	1	
Malignite	2	5	
Ischemic heart disease	2	-	
Congestive heart disease	-	2	
2 systemic disease	13	7	
≥3 systemic disease	3	4	
None	3	6	
PaO_2/FiO_2 ratio	131.98±40.93	191.40±86.69	0.001
Angiotensin II (pg/ml, mean±SD)	951.43±359.91	512.70±294.59	0.001*
ATR-I (ng/ml, mean±SD)	0.62±0.23	0.55±0.19	0.229
ATR-II (ng/ml, mean±SD)	0,94±0.27	0.93±0.10	0.778
CRP (mg/dL, mean±SD)	6.90±5.45	12.51±8.47	0.003*
Procalcitonin (ng/ml, mean±SD)	1.35±3.85	16.26±31.06	0.010*
IL-6 (pg/ml, mean±SD)	60.56±58.55	547.52±1225.45	0.034*
Ferritin (ng/ml, mean±SD)	593.15±426.30	522.44±443.73	0.369
Fibrinogen (mg/dl, mean±SD)	394.06±201.44	453.00±234.35	0.482
D-dimer (mg/L, mean±SD)	18.32±70.45	4.72±3.13	0.617

P<0.05, APACHE II: Acute Physiology, Assessment and Chronic Health Evaluation II, ATR-1: angiotensin II receptor 1; ATR-2: angiotensin II receptor 2; COPD: Chronic obstructive pulmonary disease; CRP: c-reactive protein; HFNC/NIV: High-flow nasal cannula oxygenation / noninvasive ventilation; IL-6: interleukin-6; PaO_2/FiO_2 ratio: partial arterial oxygen pressure to fractional inspired oxygen; proBNP: pro-brain natriuretic peptide; SOFA: The Sequential Organ Failure Assessment; WBC: White blood count

Table 2. Comparison of surviving and nonsurviving patients with COVID.

	Survivor (n=11)	Non-survivor (n=20)	P value
Age (year, mean±SD)	63.64±14.83	75.20±14.11	0.039*
Gender (M/F)	7.4	11.9	0.641
APACHE score (mean±SD)	14.18±6.49	22.40±5.07	0.001*
SOFA score (mean±SD)	5.00±3.03	8.70±2.96	0.004
Vasopressor	1.10	9.11	0.041*
Ventilation			
Nasal cannula	0	3	0.001*
HFNC/NIV	10	4	
Invasive mechanical ventilation	1	13	
Steroid using	11.11	18/20	0.409
Co-existing disease			
Hypertension	2	1	0.389
Diabetes mellitus	1	5	
Malignite	-	2	
Ischemic heart disease	-	2	
Congestive heart disease	-	-	
2 systemic disease	6	7	
≥3 systemic disease	1	2	
None	2	1	
PaO_2/FiO_2 ratio	115.91±27.37	140.82±44.94	0.153
Angiotensin II (pg/ml, mean±SD)	1082.53±300.35	879.33±376.34	0.200
ATRI (ng/ml, mean±SD)	0.43±0.24	0.57±0.24	0.016*
ATRII (ng/ml, mean±SD)	0,93±0.32	0.90±0.33	0.301
CRP (mg/dL, mean±SD)	8.92±6.33	5.79±4.71	0.200
Procalcitonin (ng/ml, mean±SD)	0.37±0.42	1.90±4.74	0.223
IL-6 (pg/ml, mean±SD)	69.52±73.71	55.37±49.26	1.000
Ferritin (ng/ml, mean±SD)	560.40±499.59	612.11±391.26	0.519
Fibrinogen (mg/L, mean±SD)	556.97±174.49	299.74±151.17	0.001*
D-dimer (mg/L, mean±SD)	1.49±1.26	28.05±87.89	0.004*
HS-troponine (pg/ml, mean±SD)	13.86±12.65	66.40±63.57	0.035*

*p<0.05. APACHE II: Acute Physiology, Assessment and Chronic Health Evaluation II, ATR-1: angiotensin II receptor 1; ATR-2: angiotensin II receptor 2; COPD: Chronic obstructive pulmonary disease; CRP: c-reactive protein; HFNC/NIV: High-flow nasal cannula oxygenation /noninvasive ventilation; IL-6: interleukin-6; PaO2/FiO2 ratio: partial arterial oxygen pressure to fractional inspired oxygen; proBNP: pro-brain natriuretic peptide; SOFA: The Sequential Organ Failure Assessment; WBC: White blood count

patients in the COVID group were using methylprednisolone, and none of the patients in the non-COVID group used steroids. While the rates of invasive mechanical ventilation support were similar, the use of high-flow nasal cannula (HFNC)/noninvasive mechanical ventilation (NIV) was significantly higher in the COVID group. The PaO_2/FiO_2 ratio was significantly lower in the COVID group than in the non-COVID group (p<0.05) (Table 1).

Angiotensin II level was found to be significantly higher in patients with COVID-19 than in non-COVID patients (p<0.05). There were no significant differences between the groups in terms of ATR1 and ATR2. Procalcitonin, CRP, and IL-6 levels were significantly higher in non-COVID patients than in patients with COVID-19 (p<0.05) (Table 1).

When patients with COVID were divided into surviving and non-surviving, with 11 being survivors and 20 being non-survivors, age, APACHE II and SOFA scores, vasopressor use, and need for invasive mechanical ventilation were significantly higher in non-survivors (p<0.05). An insignificantly lower angiotensin II level was observed in non-survivors compared to survivors (p>0.05). ATR1 receptor, D-dimer, and HS-troponin levels were significantly higher in non-survivors compared to survivors (p<0.05). Fibrinogen levels were significantly lower in non-survivors (p<0.05) (Table 2). There were no significant differences between any of the parameters in the surviving or nonsurviving non-COVID patients (p>0.05).

A negative correlation was observed between angiotensin II levels and procalcitonin in patients with COVID (r= -0.445, p=0.012). A positive correlation was observed between ATR1 and procalcitonin (0.459, p=0.009), APACHE II score (0.421, p=0.018), and SOFA score (0.511, p=0.003). A significant negative correlation was found between angiotensin II level and procalcitonin levels in non-COVID patients (-0.485, p=0.007).

Discussion

RAS is a complex and dynamic biaxial molecular cascade found in almost all organ systems and has an important role in neural, pulmonary, renal, cardiovascular and immune homeostasis [10]. The classical axis, ACE, includes angiotensin II and AT1R, while the counter-regulatory axis ACE2 creates the Ang-(1–7) and Mas receptor (MasR) [10]. Sepsis and SARS-CoV-2 infection are thought to cause changes in RAS. In our study, some mediators, especially angiotensin II levels, were compared in patients with viral sepsis due to COVID-19 and non-COVID patients with bacterial sepsis.

While there was no significant difference between the groups in terms of invasive mechanical ventilation use in our study, it was observed that the PaO2/FiO2 ratio was lower and HFNC/NIV use was higher in patients with COVID. Low PaO2/FiO2 ratio, high HFNC/NIV use, and high steroid use in patients with COVID-19 were thought to be related to respiratory failure and ARDS due to COVID-19. ARDS and the need for mechanical ventilation are the most common reasons for hospitalization in the intensive care unit in patients with COVID-19 [11,12]. In fact, although more invasive mechanical ventilation was expected in the group with COVID-19 compared to the non-COVID group, no difference was found in our study. This can be explained by the inclusion of patients who were previously admitted to the intensive care unit for another reason and who later developed sepsis amongst the non-COVID patient group (bacterial sepsis).

In recent years, the number of studies investigating the relationship between sepsis and the renin-angiotensin-aldosterone system has increased. However, the studies in the literature have mainly included bacterial sepsis or septic shock cases, and reported variable results [4,5,7,13]. In our previous study that we conducted on patients with bacterial sepsis and septic shock, we observed that the angiotensin II level was higher in sepsis patients who did not develop shock compared to those who did develop shock [5]. In our other study, in which we included only patients who developed shock and divided them into two groups as catecholamine-sensitive and -resistant, we observed that angiotensin II levels remained high in catecholamine-resistant patients [6]. With the COVID-19 pandemic that emerged at the end of 2019, the detection of SARS CoV-2 virus entering the cell via the ACE2 enzyme attracted attention to the renin-angiotensin-aldosterone system in patients with COVID-19 [14,15]. It has been shown that there is no significant difference between the angiotensin

II levels of patients with and without COVID who sought emergency care with the same complaints [16]. In a study involving hospitalized patients with COVID-19, no significant difference was found between ACE and ACE2 levels between patients with and without COVID. However, it has been shown that the levels of both vasoconstrictor-acting angiotensin II and other vasodilator-acting angiotensin derivatives are decreased [17]. In another study comparing patients with and without COVID, it was shown that while ACE2 protein level and activity increased, angiotensin II and angiotensin 1-7 levels decreased [18]. In a study evaluating angiotensin II levels in patients with severe or mild COVID-19, angiotensin II levels were high in patients with severe COVID-19. It has been shown that the level of angiotensin II decreased over time in both groups, and the level of angiotensin 1-7 increased in the group with COVID-19 [19]. In the study by Xavier et al. in which they compiled studies on the course of angiotensin II in patients with COVID, they reported that the best case scenario was associated with high angiotensin II and AT-1 receptor levels, and the worst case scenario was low/stable angiotensin II and stable AT-1 level [10]. As can be seen, there are different results in the literature regarding both bacterial sepsis and COVID sepsis. However, apart from our study, there is no study yet comparing angiotensin II and its receptors between viral sepsis due to COVID-19 and bacterial sepsis. In summary, in our study, which is the first study in this field, angiotensin II level was found to be higher in patients who developed COVID-19 sepsis compared to non-COVID sepsis.

When surviving and nonsurviving patients were compared, angiotensin II levels were found to be lower in nonsurviving patients with COVID sepsis, while no significant difference was found between surviving and nonsurviving patients without COVID. While studies have shown that angiotensin II levels are low in patients with bacterial sepsis who develop shock or have a mortal course, another study has shown that there is a difference in early angiotensin II levels between surviving and nonsurviving patients but not in the late period [4,5]. Angiotensin II level was found to be lower in patients with COVID who did not survive in congruity with the worst-case scenario of Xavier et al. [10].

It has been found that the level of ATR1 decreases in bacterial sepsis and septic shock compared to non-septic patients and increases in patients who recover in the following days [5]. In addition, it was found that in catecholamine-resistant patients, unlike catecholamine-sensitive patients, ATR1 increased with angiotensin II level and had high specificity and sensitivity in detecting catecholamine-resistant patients [6]. The opinion that ATR1 constitutes a gateway to COVID-related diseases also makes the function or level of ATR1 important [20]. In our study, we determined that there was no significant difference in ATR1 and ATR2 levels between patients with bacterial sepsis and patients with viral sepsis due to COVID-19. When surviving and nonsurviving patients with COVID-19 were compared, high ATR1 receptor levels were accompanied by high D-dimer and HS-troponin levels and low fibrinogen levels in the nonsurviving. In addition, a correlation was observed between ATR1 level and procalcitonin levels and APACHE II and SOFA scores. The same correlation was not observed in patients with non-COVID sepsis. Studies have shown that there is a relationship between the severity of COVID-19 and procalcitonin levels [21,22]. It has also been reported in studies that the severity of COVID or bacterial sepsis is associated with a decrease in angiotensin II levels [4,5,10]. Therefore, the correlation between procalcitonin and angiotensin II is not surprising. High APACHE and SOFA scores and high procalcitonin levels are expected results in septic patients who die or who develop shock.

Inflammatory mediators such as procalcitonin, CRP, and IL-6 have been used in the differentiation of bacterial and viral infections or in the differentiation of infectious and non-infectious inflammation [23-25]. Consistent with the literature, in our study, CRP, procalcitonin, and IL-6 levels were higher in patients with bacterial sepsis than in patients with COVID.

Conclusion

In conclusion, in our study, which consisted of patients with similar clinical disease severity, it was observed that, unlike in bacterial sepsis, the angiotensin II level was higher in patients with COVID, and ATR1 level was higher in nonsurviving patients with COVID-19. This suggests that the renin-angiotensin cascade may be stimulated by different pathways than bacterial sepsis or the same pathways can be stimulated at different intensities in viral sepsis due to COVID-19. This is an untapped issue that needs to be clarified, and this study is valuable because it is the first study in its field. However, extensive studies are needed to fully elucidate the pathogenesis and to put these mediators into practical application.

Scientific Responsibility Statement

The authors declare that they are responsible for the article's scientific content including study design, data collection, analysis and interpretation, writing, some of the main line, or all of the preparation and scientific review of the contents and approval of the final version of the article.

Animal and human rights statement

All procedures performed in this study were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards. No animal or human studies were carried out by the authors for this article.

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Conflict of interest

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